DOCKET NO: 248336US0DIV

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:	
DAVID LEWIS ET AL	:	EX: ALSTRUM ACEVEDO, J. H.
SERIAL NO: 10/766,857	:	
FILED: JANUARY 30, 2004	:	GROUP ART UNIT: 1616
FOR: PHARMACEUTICAL AEROSOL COMPOSITION CONTAINING HFA 227 AND HFA 134a	:	

DECLARATION UNDER 37 C.F.R. ə 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

Now comes Gaetano Brambilla, who deposes and states that:

1. I am a named inventor of the above-identified application.

2. I received my Degree in Pharmacy from the Universita di Parma in the year 1979.

3. I have been employed by Chiesi Farmaceutici, S.p.A., the assignee of the above-identified application, as a researcher in the field of pharmaceuticals, since 1983.

4. A copy of my *curriculum vitae* is attached hereto and is incorporated into and is part of this declaration.

5. I am an author of 20 scientific publications in the field of pressurized metered dose inhalers.

6. I am a named inventor of 11 U.S. Patents in the field of pressurized metered dose inhalers.

7. The particle size distribution of aerosol particles is usually represented by a lognormal (Gaussian) distribution, which is, in turn, described by the mass median aerodynamic diameter (MMAD), which corresponds to the diameter of 50 % by weight of the particles, and by a geometric standard deviation (GSD). In contrast to arithmetic standard deviation, GSD is not a quantity but a factor. Powers of the geometric standard deviation are multiplied by (or divided into) the geometric mean to determine the set of values that lie within a given range of dispersion.

8. The respirable fraction of an aerosol is the percent by weight of particles having an aerodynamic particle size of less than 4.7 μm and is calculated as the ratio of the fine particle dose, *i.e.* the dose collected in the stages S3-Filter, and the mean emitted dose. Thus, 4.7 μm is only a cut-off value, and the particles collected in the stages S3-Filter could have a different distribution.

9. Accordingly, the MMAD and the respirable fraction are two distinct parameters, which are not directly correlated. As a consequence, an aerosol which has a respirable fraction comprised between 45% and 69% does not necessarily have a MMAD greater than 2 μm.

10. In fact, as it can be appreciated from the two charts reported in Figure 3, on page 294 of B. Olsson, et al., PharmaEuropa, vol. 8, N. 2, pp. 291-298, June 1996 (Olsson et al.), particles collected at various stages in which the particle diameter is less than 4.7 μm, show different particle distributions. In the chart on the left-hand side of Figure 3, most particles are collected at the Filter stage and have a very fine particle size, whereas in the chart on the right-hand side most of particles are collected at Stages 3-5 and have a greater particle size.

11. Similarly, as shown in Table 1 on page 21 of WO 98/56349, an aerosol of beclomethasone in HFA 134a and 13.0 % ethanol has a respirable fraction of 52.7 % but a

MMAD of 1.0 . In this case, the respirable fraction was calculated as the ratio of the fine particle dose of 46.2 μg to the mean emitted dose of 87.6 μg (*see*, Olsson et al., left-hand col. of page 292).

12. I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

13. Further Declarant saith not.

Gaetano Brambilla

13/11/2007

Date

PERSONAL INFORMATION

Name	**GAETANO BRAMBILLA**
Address	**VIA EMILIO LEPIDO, 18 – 43100 PARMA - ITALY**
Telephone	**+39 0521 244904 (home); +39 335 7775278 (mobile)**
Fax	**+39 0521 279510**
E-mail	**g.brambilla@chiesigroup.com**
Nationality	**Italian**
Date of birth	**23 OCTOBER 1955**

WORK EXPERIENCE

• Dates	**2007 -**
• Name and address of employer	Chiesi Farmaceutici – Parma (Italy)
• Type of business or sector	Pharmaceutical
• Occupation or position held	Director, Drug Delivery Technologies
• Main activities and responsibilities	In charge of scouting new technologies for innovative drug delivery and of designing and optimisation of drug delivery devices and formulation technology platforms

• Dates	**1999 - 2007**
• Name and address of employer	Chiesi Farmaceutici – Parma (Italy)
• Type of business or sector	Pharmaceutical
• Occupation or position held	R&D Project Leader
• Main activities and responsibilities	As Project Leader, in charge of International projects at different stages of development. Roles played: team leader, project manager, technical expert. Some of the projects are mainly outsourced to CROs located in different countries (US, UK, etc.), while others are developed internally. Some of the projects have been out-licensed to major international pharma

• Dates	**1989 – 1999**
• Name and address of employer	Chiesi Farmaceutici – Parma (Italy)
• Type of business or sector	Pharmaceutical
• Occupation or position held	Pharmaceutical Technology Department Head
• Main activities and responsibilities	As Department Head in charge of 20 more employees with technical, budgeting, and people responsibilities. The Department consisted of Formulation units and a Clinical Trial Supplies one

• Dates	**1983 – 1989**
• Name and address of employer	Chiesi Farmaceutici – Parma (Italy)
• Type of business or sector	Pharmaceutical
• Occupation or position held	Formulation scientist
• Main activities and responsibilities	As group leader in charge of developing dosage forms from feasibility studies to full industrial scale. Main dosage forms: tablets, pMDIs, syrups and drops, inhalation powders

EDUCATION AND TRAINING

• Dates	1969 – 1973
• Name and type of organisation providing education and training	*Liceo classico D'Annunzio*
• Principal subjects covered	Humanities (Italian literature, Philosophy, History, Latin, Ancient Greek)

• Title of qualification awarded	**Maturità classica**
• Dates	1973 – 1979
• Name and type of organisation providing education and training	Universitá di Parma
• Principal subjects/occupational skills covered	Physical chemistry, organic chemistry, pharmaceutical chemistry, pharmacology Experimental thesis on hplc analysis
• Title of qualification awarded	**Degree in Pharmacy**

PERSONAL SKILLS AND COMPETENCES

MOTHER TONGUE	**ITALIAN**
OTHER LANGUAGES	**ENGLISH** (FLUENT)
ORGANISATIONAL SKILLS AND COMPETENCES	PROJECT MANAGEMENT 5 more years experience on the job leading International inter-company teams; daily interactions with companies with strong project oriented culture; short courses BUDGET Management over the years of Department or Project budgets PEOPLE Over the years in charge of employees as either line or functional manager
TECHNICAL SKILLS AND COMPETENCES	PHARMACEUTICAL DEVELOPMENT AND TECHNICAL PLANNING 10 more years as head of a department of about 20 scientists dedicated to formulation development from feasibility studies to industrial scale-up INHALATION TECHNOLOGIES Co-author of many publications as in the attached publications list; Named as inventor in 17 patent families, mainly in the area of inhalation technologies; Member for the current company of EPAG (European Pharmaceutical aerosol Group) and of IPAC (International Pharmaceutical Aerosol Consortium). Regular presence to some of the most important meetings of the area.

List of Publications

Brambilla G, Ganderton D, Garzia R, Lewis D, Meakin B, Ventura P

Modulation of Aerosol Clouds Produced by HFA Solution Inhalers

Proceedings of the: "Drug Delivery to the Lungs IX of the Aerosol Society", London, 14th & 15th December 1998, p. 155-159

Lewis DA, Johnson S, Meakin BJ, Ganderton D, Brambilla G, Garzia R, Ventura P

Effects of Actuator Orifice Diameter on Beclomethasone Dipropionate Delivery from a pMDI HFA Solution Formulation

Proceedings of the: "Respiratory Drug Delivery VI", Hilton Head, South Carolina, May 3-7, 1998, p. 363-364

Brambilla G, Ganderton D, Garzia R, Lewis D, Meakin B, Ventura P

Modulation of Aerosol Clouds Produced by Pressurised Inhalation Aerosols

International Journal of Pharmaceutics, 186(1), 53-61, 1999

Lewis D, Brambilla G, Ganderton D, Howlett D, Meakin B

Through Can Life Variation in Delivered Dose from PMDIs

Proceedings of the: "Respiratory Drug Delivery VII", Palm Harbor at Tarpon Springs, Florida. May 14-18, 2000, p. 373-375

Lewis DA, Brambilla G, Ganderton D, Meakin BJ

Ipratropium Bromide HFA Solution pMDIs for the Treatment of COPD

Proceedings of the: "Respiratory Drug Delivery VII", Palm Harbor at Tarpon Springs, Florida, May 14-18, 2000, p. 369-372

Meakin BJ, Lewis DA, Ganderton D, Brambilla G

Countering Challenges Posed by Mimicry of CFC Performance Using HFA Systems

Proceedings of the: "Respiratory Drug Delivery VII", Palm Harbor at Tarpon Springs, Florida. May 14-18, 2000, p. 99-107

Davies RJ, Lewis DA, Ganderton D, Meakin BJ, Brambilla G, Murphy SD, Nicholls TR

Velocity Profiling of a New HFA Budesonide pMDI

Proceedings of the: "Respiratory Drug Delivery VIII", Tucson, Arizona, May 12-16, 2002, P. 759-762

Ganderton D, Lewis D, Davies R, Meakin B, Brambilla G, Church T

Modulite: a Means of Designing the Aerosols Generated by Pressurised Metered Dose Inhalers

Respiratory Medicine, 96(Suppl D), S3-S8, 2002

Brambilla G, Church T, Ganderton D, Lewis D, Meakin B, Richards J

A Comparative Formoterol HFA pMDI Delivery Performance from an Integral Device

Proceedings of the: "Respiratory Drug Delivery(RDD) IX", Palm Spring, California, April 25-29, 2004. P. 845-848

Lewis DA, Ganderton D, Meakin BJ, Brambilla G

Theory and Practice with Solution Systems

Proceedings of the: "Respiratory Drug Delivery(RDD) IX", Palm Spring, California, April 25-29, 2004, p. 109-116

Lewis DA, Ganderton D, Meakin B J, Brambilla G

Modulite®: A Simple Solution to a Difficult Problem

Respiration 2005, Vol 72 Supp 1, pp 3-5.

Armanni A, Brambilla G, Cocconi D, Taverna M C, Mariotti F, Meakin B J, Western K, Henton JM.

In Vitro And In Vivo Drug Delivery From The Next™ Dpi

Proceedings of the: "Respiratory Drug delivery 10th (RDD X)" Florida,USA, April 23-27, 2006. p. 561-564

Brambilla G, Armanni A, Cocconi D, Musa R, Taverna MC, Meakin B J, Western K

Formulation Development For The Next® Dpi

Proceedings of the:"Respiratory Drug Delivery 10th (RDD X)", Florida,USA, April 23-27, 2006. p. 557-
560

Brambilla G, Bodria A, Cavecchi A, Coli P, Fontani C, Labadini L

Characterization of a Carmoterol HFA Solution pMDI Formulated Using ModuliteTM Technology

Proceedings of the:" Respiratory Drug Delivery 10th (RDD X)" Florida,USA, April 23-27, 2006, pag 569-572

Brambilla G, Bodria A, Cavecchi A, Coli P, Fontani C, Labadini L

Particle Size Distribution of a Combination HFA Solution pMDI Formulated with ModuliteTM Technology

Proceedings of the:" Respiratory Drug delivery 10th (RDD X)" Florida,USA, April 23-27, 2006, pag 565-568, 2006

Brambilla G, Cocconi D, Armanni A, Smith S, Lye E, Burge S

Designing a Novel Dry Powder Inhaler: The NEXT® DPI

Proceedings of the: "Respiratory Drug delivery 10th (RDD X)" Florida,USA, April 23-27, 2006, p. 553-556

Lewis D, Brambilla G, Church T, Meakin B

Comparative In-Vitro Performance of a BDP HFA Solution MDI Using USP and Anatomical Induction Ports

Proceedings of the:"Respiratory Drug delivery 10th (RDD X)" Florida,USA, April 23-27, 2006, p. 943-946

Lewis D, Brambilla G, Church T, Meakin B

BDP and Formoterol Association within a Combination HFA Solution MDI

Proceeding of the "Respiratory Drug delivery 10th (RDD X)" Florida, USA April 23-27, 2006, p. 939-942

Lewis D A, Meakin BJ, Brambilla G

New Actuators Versus Old:Reasons and Results for Actuator Modifications for HFA Solution MDIs.

Proceedings of the : "Respiratory Drug delivery 10th (RDD X)" Florida,USA, April 23-27, 2006. p. 101-110

Acerbi D, Brambilla G, Kottakis I

Advances in Asthma and COPD Managment: Delivering CFC-Free Inhaled Therapy Using MODULITE® Technology.

Pulmonary Pharmacology and Therapeutics, 20/3 (290-303), 2007

Acerbi D, Brambilla G, Lewis D, Meakin B

Gaining Approval to Market Therapeutically Equivalent Inhalers in the EU: an Industry Perspective

Respiratory Drug Delivery Europe, 17-20 April 2007, Paris France. Pag 127-140
